



EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014. Scientific Opinion on the modification of the authorisation of a health claim related to plant sterol esters and lowering blood LDL-cholesterol; high blood LDL-cholesterol is a risk factor in the development of (coronary) heart disease pursuant to Article 14 of Regulation (EC) No 1924/2006, following a request in accordance with Article 19 of Regulation (EC) No 1924/2006

EFSA Publication

Link to article, DOI:
[10.2903/j.efsa.2014.3577](https://doi.org/10.2903/j.efsa.2014.3577)

Publication date:
2014

Document Version
Publisher's PDF, also known as Version of record

[Link back to DTU Orbit](#)

Citation (APA):
EFSA Publication (2014). *EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014. Scientific Opinion on the modification of the authorisation of a health claim related to plant sterol esters and lowering blood LDL-cholesterol; high blood LDL-cholesterol is a risk factor in the development of (coronary) heart disease pursuant to Article 14 of Regulation (EC) No 1924/2006, following a request in accordance with Article 19 of Regulation (EC) No 1924/2006*. European Food Safety Authority. the EFSA Journal Vol. 12(2) No. 3577 <https://doi.org/10.2903/j.efsa.2014.3577>

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

SCIENTIFIC OPINION

Scientific Opinion on the modification of the authorisation of a health claim related to plant sterol esters and lowering blood LDL-cholesterol; high blood LDL-cholesterol is a risk factor in the development of (coronary) heart disease pursuant to Article 14 of Regulation (EC) No 1924/2006, following a request in accordance with Article 19 of Regulation (EC) No 1924/2006¹

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)^{2, 3}

European Food Safety Authority (EFSA), Parma, Italy

This scientific opinion, published on 13 May 2014, replaces the earlier version published on 20 February 2014*

ABSTRACT

Following an application from SANOFI-AVENTIS FRANCE, submitted pursuant to Article 19 of Regulation (EC) No 1924/2006 via the Competent Authority of France, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the modification of the authorisation of a health claim related to plant sterol esters and lowering blood LDL-cholesterol (high blood LDL-cholesterol is a risk factor in the development of (coronary) heart disease), pursuant to Article 14 of Regulation (EC) No 1924/2006. The applicant requested an extension of the conditions of use to powder supplements to be diluted in water at a dose of 2 g per day, which would lower blood LDL-cholesterol concentrations by “5.4-8.1 %” after six weeks of daily consumption. Plant sterol esters are sufficiently characterised. Lowering blood LDL-cholesterol concentrations is a beneficial physiological effect and elevated blood LDL-cholesterol concentration is a risk factor for coronary heart disease. The target population is subjects who need and want to lower their blood cholesterol. In weighing the evidence, the Panel took into account that only one human intervention study showed a reduction in blood LDL-cholesterol concentrations after six weeks of consuming 2 g/day of plant sterol esters in powder, the large uncertainty surrounding the estimates of this effect, and that the results of that study have not been replicated in

¹ On request from the Competent Authority of France following an application by SANOFI-AVENTIS FRANCE, Question No EFSA-Q-2013-00595, adopted on 5 February 2014.

² Panel members: Carlo Agostoni, Roberto Berni Canani, Susan Fairweather-Tait, Marina Heinonen, Hannu Korhonen, Sébastien La Vieille, Rosangela Marchelli, Ambroise Martin, Androniki Naska, Monika Neuhäuser-Berthold, Grażyna Nowicka, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Martin Stern, Sean (J.J.) Strain, Inge Tetens, Daniel Tomé, Dominique Turck and Hans Verhagen. One member of the Panel did not participate in the discussion on the subject referred to above because of potential conflicts of interest identified in accordance with the EFSA policy on declarations of interests. Correspondence: nda@efsa.europa.eu

³ Acknowledgement: The Panel wishes to thank the members of the Working Group on Claims: Carlo Agostoni, Jean-Louis Bresson, Susan Fairweather-Tait, Marina Heinonen, Ambroise Martin, Hildegard Przyrembel, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Sean (J.J.) Strain, Inge Tetens, Hendrik Van Loveren, and Peter Willatts for the preparatory work on this scientific opinion.

* Minor changes of editorial nature were made. The changes do not affect the contents of this report. To avoid confusion, the original version of the opinion has been removed from the website, but is available on request, as is a version showing all the changes made.

Suggested citation: EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014. Scientific Opinion on the modification of the authorisation of a health claim related to plant sterol esters and lowering blood LDL-cholesterol; high blood LDL-cholesterol is a risk factor in the development of (coronary) heart disease pursuant to Article 14 of Regulation (EC) No 1924/2006, following a request in accordance with Article 19 of Regulation (EC) No 1924/2006. EFSA Journal 2014;12(2):3577, 14 pp. doi:10.2903/j.efsa.2014.3577

Available online: www.efsa.europa.eu/efsajournal

other studies. The Panel reiterates its previous conclusion that, while plant sterols added to foods such as margarine-type spreads, mayonnaise, salad dressings, and dairy products have been shown consistently to lower blood LDL-cholesterol concentrations in a large number of studies, the effective dose of plant sterols (as powder diluted in water) needed to achieve a given magnitude of effect in a given timeframe cannot be established with the data provided.

KEY WORDS

plant sterol esters, powder, coronary heart disease, LDL-cholesterol

SUMMARY

Following an application from SANOFI-AVENTIS FRANCE, submitted pursuant to Article 19 of Regulation (EC) No 1924/2006 via the Competent Authority of France, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver an opinion on the modification of the authorisation of a health claim related to plant sterol esters and lowering blood LDL-cholesterol (high blood LDL-cholesterol is a risk factor in the development of (coronary) heart disease), pursuant to Article 14 of Regulation (EC) No 1924/2006, which was authorised by Regulation (EC) No 376/2010 amending Regulation (EC) No 983/2009 and Regulation (EC) No 384/2010.

The applicant requested an extension of the conditions of use to an additional food matrix (i.e. powder supplements to be diluted in water) at a dose of 2 g per day, and which would lower blood LDL-cholesterol concentrations by “5.4-8.1 %” after six weeks of daily consumption.

The application included a request for the protection of proprietary data.

The Panel considers that plant sterol esters, the food constituents which are the subject of the health claim, are sufficiently characterised.

The Panel considers that lowering blood LDL-cholesterol concentrations is a beneficial physiological effect, and that elevated blood LDL-cholesterol concentration is a risk factor for coronary heart disease. The target population is subjects who need and want to lower their blood cholesterol.

The applicant identified one unpublished study as being pertinent to the health claim.

In this multi-centre, double-blind, placebo-controlled study, 253 subjects were randomised to consume a powder with either plant sterol esters at doses of 2 g/day (n = 86) or 2.4 g/day (n = 86), or placebo (n = 81), at the two main meals of the day for six weeks. The primary outcome was changes in LDL-cholesterol (LDL-c) concentrations between the intervention groups and placebo.

The analyses of the primary outcomes were presented for all randomised subjects (intention to treat, ITT), for the population of completers (n = 213) and for the per protocol (PP) population (n = 161).

Compared with placebo, LDL-c concentrations in the 2 g/day group significantly decreased by 8.22 ± 3.61 mg/dL (95 % CI: 1.11, 15.32; $p = 0.0235$) in the ITT population, by 8.08 ± 4.09 mg/dL (95 % CI: 0.02, 16.13; $p = 0.0494$) in the population of completers, and by 11.40 ± 4.84 mg/dL (95 % CI: 1.84, 20.97; $p = 0.0197$) in the PP population. Differences in changes of LDL-c concentrations during the study between the two intervention groups were not statistically significant.

The Panel notes that this study shows a significant reduction in LDL-c concentrations of 4.8 % (95 % CI: 0.46 %, 9.64 %), 5.4 % (95 % CI: 0.2 %, 11.1 %) and 7.4 % (95 % CI: 0.5 %, 14.3 %) in the different populations analysed (ITT, population of completers and PP population, respectively), during continuous consumption of plant sterol esters in powder for six weeks at doses of 2 g/day.

The applicant also provided three human intervention studies as being supportive of the health claim. These studies investigated the effect of various types of phytosterols in different formats which did not comply with the specifications provided by the applicant for the extension of the conditions of use. The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of the extension of the conditions of use proposed by the applicant.

A meta-analysis including the four intervention studies mentioned above was provided by the applicant as being supportive of the health claim. The Panel notes that this meta-analysis includes only one study carried out with the food and matrix for which the extension of the conditions of use is requested, and thus it does not provide additional information for the scientific substantiation of the extension of the conditions of use to plant sterol esters in powder.

In weighing the evidence, the Panel took into account that only one human intervention study showed a reduction in blood LDL-c concentrations of 4.8 % (95 % CI: 0.46 %, 9.64 %), 5.4 % (95 % CI: 0.2 %, 11.1 %) and 7.4 % (95 % CI: 0.5 %, 14.3 %) in the different populations analysed after six weeks of consuming 2 g/day of plant sterol esters in powder, the large uncertainty surrounding the estimates of this effect, and that these results have not been replicated in other studies.

The Panel reiterates its previous conclusion that, while plant sterols added to foods such as margarine-type spreads, mayonnaise, salad dressings, and dairy products such as milk, yoghurts, including low-fat yoghurts, and cheese have been shown consistently to lower blood LDL-c concentrations in a large number of studies, the effective dose of plant sterols (as powder diluted in water) needed to achieve a given magnitude of effect in a given timeframe, cannot be established with the data provided.

TABLE OF CONTENTS

Abstract	1
Summary	3
Table of contents	5
Background	6
Background	6
Terms of reference	7
EFSA Disclaimer.....	7
Information provided by the applicant	8
Assessment	9
1. Characterisation of the food/constituent	9
2. Relevance of the claimed effect to human health.....	9
3. Scientific substantiation of the claimed effect	9
Conclusions	12
Documentation provided to EFSA	13
References	13
Abbreviations	14

BACKGROUND

Regulation (EC) No 1924/2006⁴ harmonises the provisions that relate to nutrition and health claims, and establishes rules governing the Community authorisation of health claims made on foods. As a rule, health claims are prohibited unless they comply with the general and specific requirements of this Regulation, are authorised in accordance with this Regulation and are included in the lists of authorised claims provided for in Articles 13 and 14 thereof. In particular, Articles 14 to 17 of this Regulation lay down provisions for the authorisation and subsequent inclusion of reduction of disease risk claims and claims referring to children's development and health in a Community list of permitted claims.

The same Regulation, as referred to in Article 19, also lays down provisions for modification, suspension and revocation of authorisations. The procedures laid down in Article 15 and 18 shall apply *mutatis mutandis*.

According to Article 15 of that Regulation, an application for the modification, suspension or revocation of authorisations of health claims included in the Community list of permitted claims referred shall be submitted by the applicant to the national competent authority of a Member State, who will make the application and any supplementary information supplied by the applicant available to the European Food Safety Authority (EFSA).

STEPS TAKEN BY EFSA

- The application was received on 10/06/2013.
- The scope of the application was proposed to fall under a health claim referring to disease risk reduction.
- On 10/07/2013, during the validation process of the application, EFSA sent a request to the applicant asking it to provide missing information.
- On 22/07/2013, EFSA received the missing information as submitted by the applicant.
- The scientific evaluation procedure started on 24/07/2013.
- On 25/09/2013, the Working Group on Claims of the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application, and the clock was stopped on 08/10/2013 in compliance with Art. 16(1) of Regulation (EC) No 1924/2006.
- On 29/10/2013, EFSA received the requested information as submitted by the applicant and the clock was restarted.
- On 22/11/2013, the Working Group on Claims of the NDA Panel agreed on a list of questions for the applicant to provide additional information to accompany the application and the clock was stopped on 04/12/2013 in compliance with Art. 16(1) of Regulation (EC) No 1924/2006.
- On 03/01/2014, EFSA received the requested information as submitted by the applicant and the clock was restarted.
- During its meeting on 05/02/2014, the NDA Panel, after having evaluated the overall data submitted, adopted an opinion on the scientific substantiation of a health claim related to plant sterol esters and lowering blood LDL-cholesterol under the new conditions of use proposed by the applicant.

⁴ Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods. OJ L 404, 30.12.2006, p. 9–25.

TERMS OF REFERENCE

EFSA is requested to evaluate the scientific data submitted by the applicant in accordance with Article 19 of Regulation (EC) No 1924/2006. On the basis of that evaluation, EFSA will issue an opinion on the modification of the authorisation of a health claim related to plant sterol esters and lowering blood LDL-cholesterol; high blood LDL-cholesterol is a risk factor in the development of (coronary) heart disease, which was authorised by Regulation (EC) No 376/2010 amending Regulation (EC) No 983/2009 and Regulation (EC) No 384/2010..

EFSA DISCLAIMER

The present opinion does not constitute, and cannot be construed as, an authorisation to the marketing of plant sterol esters, a positive assessment of their safety, nor a decision on whether plant sterol esters are, or are not, classified as a foodstuff. It should be noted that such an assessment is not foreseen in the framework of Regulation (EC) No 1924/2006.

It should also be highlighted that the scope, the proposed wording of the claim, and the conditions of use as proposed by the applicant may be subject to changes, pending the outcome of the authorisation procedure foreseen in Article 17 of Regulation (EC) No 1924/2006.

INFORMATION PROVIDED BY THE APPLICANT

Applicant's name and address: SANOFI-AVENTIS FRANCE, 9 Boulevard Romain Rolland, 75159, Paris, Cedex 14, France.

The application includes confidential and proprietary data. The applicant claims confidentiality and proprietary rights for the unpublished study report by Bruckert (2012) and the unpublished meta-analysis by Cucherat (2013). The applicant also claimed confidentiality rights for information pertaining to the manufacturing process.

Food/constituent as stated by the applicant

According to the applicant, the food constituent that is the subject of the health claim is plant sterol esters presented as a food supplement in a powder sachet. Plant sterols are esterified with food-grade fatty acids of vegetable oil origin.

The applicant has provided the composition of plant sterol esters for which the health claim is made, and which has been authorised under the Novel Food Regulation EC 258/97, for the placing on the market of various products with added phytosterols/phytosterols (Decision 2000/500/EC, 2004/333-336/EC, 2004/845/EC, 2006/58-59/EC, 2007/343/EC and 2008/36/EC): β -sitosterol < 80 %, β -sitostanol < 15 %, campesterol < 40 %, campestanol < 5 %, stigmasterol < 30 %, brassicasterol < 3 %, and other phytosterols < 3 %.

In the context of this dossier, the quantities of plant sterol esters are expressed as equivalent weights of free (unesterified) sterols.

Health relationship as claimed by the applicant

According to the applicant, the claimed effect concerns the reduction effect size in blood low density lipoprotein-cholesterol (LDL-c) with the consumption of plant sterol esters presented as a food supplement in a powder sachet. Blood concentration of LDL-c is the outcome measured to assess the claimed effect in humans. Elevated blood LDL-c is a risk factor for coronary heart disease (CHD), which is an important cause of mortality and morbidity. Lowering LDL-c by dietary intervention has been shown to reduce the risk of coronary heart disease. Lowering LDL-c is considered by the EFSA NDA Panel as beneficial to human health in its scientific opinions (EFSA, 2008a, b, 2009a).

Wording of the health claim as proposed by the applicant

The applicant has proposed the following wording for the health claim: "Plant sterol esters presented as food supplement in powder sachet have been shown to lower/reduce blood cholesterol. High cholesterol is a risk factor in the development of coronary heart disease".

Specific conditions of use as proposed by the applicant

According to the applicant, the target population for which the health claim is requested are people with mildly raised blood LDL-c concentration who need and want to lower their blood cholesterol. Patients on cholesterol-lowering medication should consume the product only under medical supervision (EFSA, 2008a, b, 2009a).

The applicant has proposed new conditions of use to obtain the claimed effect:

- the consumption of a daily intake of 2.0 g of plant sterol esters (expressed as the weight of free equivalents) presented as food supplement in powder sachet, which can reasonably be part of a balanced diet due to a very low calorie intake of this matrix;
- when referring to the magnitude of the effect, the range “5.4-8.1 %” and the duration of consumption of six weeks to obtain the effect will be communicated to the consumer.

Specific statements shall be addressed according to the Commission Regulation (EC) No. 608/2004 concerning the labelling of foods and food ingredients with added phytosterols, phytosterol esters, phytostanols and/or phytostanol esters.

ASSESSMENT

The applicant proposed a change in the conditions of use for claims made on food products with added plant sterol esters as authorised by Regulation (EC) No 376/2010, amending Regulation (EC) 983/2009, and Regulation (EC) No 384/2010. The authorised claim is: “Plant sterols/plant stanol esters have been shown to lower/reduce blood cholesterol. High cholesterol is a risk factor in the development of coronary heart disease”. The conditions of use of the claim are: “Information to the consumer that the beneficial effect is obtained with a daily intake of 1.5-2.4 g plant sterols/stanols. Reference to the magnitude of the effect may only be made for foods within the following categories: yellow fat spreads, dairy products, mayonnaise and salad dressings. When referring to the magnitude of the effect, the entire range “7 to 10 %” and the duration to obtain the effect “in 2 to 3 weeks” must be communicated to the consumer”.

The applicant requested an extension of the conditions of use to an additional food matrix (i.e. powder supplements to be diluted in water) at a dose of 2 g per day, and which would lower blood LDL-cholesterol (LDL-c) concentrations by “5.4-8.1 %” after six weeks of daily consumption.

1. Characterisation of the food/constituent

The food constituent that is the subject of the health claim is plant sterol esters from natural sources with a composition as specified in the Commission Decisions authorising the placing on the market of food products with added plant sterols under Regulation (EC) No 258/97 (Commission Decisions 2000/500/EC, 2004/333-336/EC, 2004/845/EC, 2006/58-59/EC, 2007/343/EC and 2008/36/EC) and subsequent products authorised under Regulation (EC) No 258/97 for the placing on the market of products with added plant sterols.

The Panel considers that plant sterol esters, the food constituents for which the health claim is proposed, are sufficiently characterised.

Throughout this opinion, quantities of plant sterols esters are expressed as the equivalent weights of free [i.e. non-esterified] sterols.

2. Relevance of the claimed effect to human health

The Panel considers that lowering blood LDL-c concentrations is a beneficial physiological effect, and that elevated blood LDL-c is a risk factor for coronary heart disease (EFSA, 2008a, b, 2009a). The target population is subjects who need and want to lower their blood cholesterol.

3. Scientific substantiation of the claimed effect

The scientific substantiation of this claim focuses on the efficacy of 2 g per day of plant sterol esters in powder on LDL-c lowering and on the minimum duration of the intervention for the effect to occur.

The applicant performed a literature search in PubMed and NCBI databases, without applying any time restrictions, by combining specific search terms related to “phytosterols”, “powder” and “food supplement”. No publications related to the use of plant sterol esters in powder were retrieved through the literature search.

The applicant provided an unpublished study report (Bruckert, 2012) on the effect of plant sterol esters in powder on blood LDL-c concentrations.

The multi-centre, randomised, double-blind, placebo-controlled study by Bruckert (2012) investigated the effect of two doses (2 g/day and 2.4 g/day) of plant sterol esters in powder on blood LDL-c concentrations in subjects with LDL-c concentrations ≥ 160 mg/dL. Subjects on cholesterol-lowering medications, and subjects who had consumed phytosterols as food supplements or as enriched foods within the six weeks prior to enrolment, were excluded from the study. At the screening visit blood samples were collected for a serum lipid assay performed in a local laboratory, unless subjects had a lipid test performed less than three months before the visit.

A total of 253 subjects meeting the inclusion criteria were randomised to consume either plant sterol esters at doses of 2 g/day ($n = 86$) or 2.4 g/day ($n = 86$) or placebo ($n = 81$). The study products were provided as powder in sachets containing 1 g or 1.2 g of plant sterol esters, or a mixture of skimmed milk powder and maltodextrin (placebo), and were consumed twice a day at the two main meals for 42 consecutive days. Fasting blood samples were collected at baseline and on day 43 of the study (assays performed in a central laboratory). Compliance was evaluated by counting the remaining sachets at the final visit.

Power calculations were performed assuming an 8 % difference in LDL-c concentrations between the two intervention groups and placebo, a mean baseline LDL-c concentration of 175 mg/dL and a SD of 23 mg/dL, a dropout rate of 5 %, a power of 90 % and $\alpha = 0.025$. It was calculated that 70 subjects per group would be needed to detect differences in LDL-c changes between the intervention groups and placebo, and that 74 subjects per group would be required to detect differences between the two intervention groups (secondary outcome). The primary outcome of the study was changes in LDL-c concentrations between the intervention groups and placebo. Secondary outcomes were changes in blood concentrations of high-density lipoprotein-cholesterol (HDL-c), total cholesterol, triglycerides and phytosterols (lathosterol, sitosterol, campesterol).

Among the 253 subjects randomised, seven (two in each intervention group and three in the placebo group) did not take the study products, two subjects in the 2 g/day group were excluded owing to administrative violations, and 31 subjects (nine in the 2 g/day group, 14 in the 2.4 g/day group, and eight in the placebo group) were excluded because LDL-c concentrations were not available either at baseline ($n = 14$), at the end of the study ($n = 14$) or at both time points ($n = 3$). Upon a request by EFSA for clarification on the missing values, the applicant indicated that missing values for LDL-c analysed by the central study laboratory, either at baseline or at the end of the study, was a pre-planned exclusion criterion; that the characteristics of subjects excluded for this reason were comparable across study groups and between the subjects retained and excluded, and thus the distribution of missing data could be assumed to be at random; and that any method used post-hoc for imputing missing values would have been more prone to bias than the exclusion of subjects as planned. Two subjects in each intervention group and five subjects in the placebo group had < 80 % compliance with the study products.

The analyses of the primary and secondary outcomes were presented for the population of completers ($n = 213$; 73 subjects in the 2 g/day group, 70 subjects in the 2.4 g/day and placebo groups) and for the per protocol (PP) population ($n = 161$; 58 subjects in the 2 g/day group, 52 subjects in the 2.4 g/day group, and 51 subjects in the placebo group). The study groups were not significantly different at baseline regarding age, sex, body mass index (BMI) or LDL-c concentrations.

Differences between each intervention group and placebo regarding changes in LDL-c concentrations during the study were assessed by using analysis of covariance (ANCOVA) adjusting for baseline LDL-c concentrations (primary analysis). An explanatory analysis comparing the 2 g/day vs. the 2.4 g/day group was also planned by using the same model as for the primary analysis. Results were given as mean differences \pm SD and 95 % CI.

Compared with placebo, LDL-c concentrations significantly decreased by 8.08 ± 4.09 mg/dL in the 2 g/day group (95 % CI: 0.02, 16.13; $p = 0.0494$) and by 10.12 ± 4.12 mg/dL in the 2.4 g/day group (95 % CI: 1.99, 18.25; $p = 0.0150$) in the population of completers. LDL-c concentrations also decreased significantly in the 2 g/day group (by 11.40 ± 4.84 ; 95 % CI: 1.84, 20.97; $p = 0.0197$) and in the 2.4 g/day group (by 13.83 ± 4.97 ; 95 % CI: -4.02, 23.64; $p = 0.0060$) compared with placebo when the PP population was considered. Differences in changes of LDL-c concentrations between the two intervention groups were not statistically significant. Upon a request by EFSA for clarification on the statistical analyses, the applicant provided a statistical analysis of the differences between each intervention group and placebo regarding changes in LDL-c concentrations including all subjects who were randomised (ITT, intention to treat). The analysis was performed using an ANCOVA model adjusted for baseline, and by replacing the missing data with the median value of completers. Compared with placebo, LDL-c concentrations significantly decreased by 8.22 ± 3.61 mg/dL in the 2 g/day group (95 % CI: 1.11, 15.32; $p = 0.0235$) and by 8.64 ± 3.58 mg/dL in the 2.4 g/day group (95 % CI: 1.58, 15.70; $p = 0.0166$).

Results were also provided as percent changes from baseline. In the ITT population LDL-c concentrations decreased by 4.8 % (95 % CI: 0.46 %, 9.64 %) in the 2 g/day group and by 4.8 % (95 % CI: 0.00 %, 9.63 %) in the 2.4 g/day group compared with placebo. In the population of completers, LDL-c concentrations decreased by 5.4 % (95 % CI: 0.2 %, 11.1 %) in the 2 g/day group and by 5.5 % (95 % CI: 0.2 %, 11.3 %) in the 2.4 g/day group compared with placebo. In the PP population, LDL-c concentrations decreased by 7.4 % (95 % CI: 0.5 %, 14.3 %) in the 2 g/day group and by 7.5 % (95 % CI: 0.4 %, 14.6 %) in the 2.4 g/day group compared with placebo.

An additional sub-group analysis was performed in the PP population to calculate differences in the percentage change of LDL-c between the intervention groups and placebo, which included only 96 subjects with LDL-c concentrations ≥ 160 mg/dL at baseline as measured in the central laboratory (38% of the recruited subjects). During the evaluation process, EFSA requested the applicant to explain how this sub-group analysis could be used to estimate the effect of plant sterol esters at the proposed dose for the target population (i.e. subjects who need and want to lower their blood cholesterol). In the reply, and with reference to Regulation 718/2013, which foresees that products with added phytosterols, phytosterol esters, phytosterols and/or phytosterol esters, are not intended for people who do not need to control their blood cholesterol, the applicant explained that subjects with LDL-c concentrations < 160 mg/dL at baseline as measured in the central laboratory could be considered as people who do not need to control their blood cholesterol. The Panel notes that LDL-c concentrations < 160 mg/dL at baseline as measured in the central laboratory was not a criterion for stratifying subjects at randomisation. The Panel considers that this sub-group analysis cannot be used to estimate the effect of plant sterol esters at the proposed dose (2 g/day) for the target population, in which blood cholesterol concentrations are generally assessed as in the recruitment phase of this study.

The Panel notes that this study shows a significant reduction in LDL-c concentrations of 4.8 % (95 % CI: 0.46 %, 9.64 %), 5.4 % (95 % CI: 0.2 %, 11.1 %) and 7.4 % (95 % CI: 0.5 %, 14.3 %) in the different populations analysed (ITT, population of completers and PP population, respectively), during continuous consumption of plant sterol esters in powder for six weeks at doses of 2 g/day.

Three additional human intervention studies were identified by the applicant through the literature search as being supportive of the health claim (McPherson et al., 2005; Carr et al., 2009; Maki et al., 2012). The Panel notes that these studies investigated the effect of various types of phytosterols (i.e.

esterified or free sterols and stanols, stanol-lecithin complex) in different formats (i.e. tablets or capsules), which do not comply with the specifications provided by the applicant for the extension of the conditions of use (i.e., plant sterol esters in powder). The Panel considers that no conclusions can be drawn from these studies for the scientific substantiation of the extension of the conditions of use proposed by the applicant.

The applicant also provided an unpublished meta-analysis (Cucherat, 2013), which included the unpublished study by Bruckert (2012) and the three intervention studies which were retrieved through the literature search (McPherson et al., 2005; Carr et al., 2009; Maki et al., 2012).

The Panel notes that the meta-analysis by Cucherat (2013) includes only one study (Bruckert, 2012) carried out with the food and matrix for which the extension of the conditions of use is requested. In this respect, EFSA invited the applicant to comment on how this meta-analysis could provide evidence for an extension of the conditions of use to plant sterol esters in powder for at the dose and for the size of the effect proposed. The applicant indicated that the meta-analysis was conducted to highlight that the evidence available is not sufficient to extend the conditions of use for the claim to dry extract supplements other than the power sachets. The Panel considers that this meta-analysis does not provide additional information for the scientific substantiation of the extension of the conditions of use to plant sterol esters in powder.

In weighing the evidence, the Panel took into account that only one human intervention study showed a reduction in blood LDL-c concentrations of 4.8 % (95 % CI: 0.46 %, 9.64 %), 5.4 % (95 % CI: 0.2 %, 11.1 %) and 7.4 % (95 % CI: 0.5 %, 14.3 %) in the different populations analysed after six weeks of consuming 2 g/day of plant sterol esters in powder, the large uncertainty surrounding the estimates of this effect, and that these results have not been replicated in other studies.

The Panel reiterates its previous conclusion (EFSA, 2009b) that, while plant sterols added to foods such as margarine-type spreads, mayonnaise, salad dressings, and dairy products such as milk, yoghurts, including low-fat yoghurts, and cheese have been shown consistently to lower blood LDL-cholesterol concentrations in a large number of studies, the effective dose of plant sterols (as powder diluted in water) needed to achieve a given magnitude of effect in a given timeframe, cannot be established with the data provided.

CONCLUSIONS

On the basis of the data presented, the Panel concludes that:

- The food constituents, plant sterol esters, which are the subject of the health claim, are sufficiently characterised.
- Lowering of blood LDL-cholesterol concentrations is a beneficial physiological effect; an elevated blood LDL-cholesterol concentration is a risk factor for coronary heart disease.
- While plant sterols added to foods such as margarine-type spreads, mayonnaise, salad dressings, and dairy products such as milk, yoghurts, including low-fat yoghurts, and cheese have been shown consistently to lower blood LDL-cholesterol concentrations in a large number of studies, the effective dose of plant sterols (as powder diluted in water) needed to achieve a given magnitude of effect in a given timeframe, cannot be established with the data provided.

DOCUMENTATION PROVIDED TO EFSA

Health claim application on plant sterol esters and lowering blood LDL-cholesterol (high blood LDL-cholesterol is a risk factor in the development of (coronary) heart disease) pursuant to Article 14 of Regulation (EC) No 1924/2006 following a request in accordance with Article 19 of the aforementioned Regulation (Claim serial No: 0389_FR). June 2013. Submitted by SANOFI-AVENTIS FRANCE.

REFERENCES

- Bruckert E, 2012 (unpublished, claimed as proprietary and confidential by the applicant). "A comparative study assessing the effect of two dosages of a food supplement containing phytosterol esters versus placebo on concentrations of LDL-cholesterol".
- Carr TP, Krogstrand KL, Schlegel VL and Fernandez ML, 2009. Stearate-enriched plant sterol esters lower serum LDL cholesterol concentration in normo- and hypercholesterolemic adults. *The Journal of Nutrition*, 139, 1445-1450.
- Cucherat M, 2013 (unpublished, claimed as proprietary and confidential by the applicant). "Phytosterols dry extract food supplements: meta-analysis of randomized clinical trials".
- EFSA (European Food Safety Authority), 2008a. Scientific Opinion of the Panel on Dietetic Products, Nutrition and Allergies on a request from McNeil Nutritionals Ltd. related to the scientific substantiation of a health claim on plant stanol esters and lower/reduced blood cholesterol and reduced risk of (coronary) heart disease pursuant to Article 14 of Regulation (EC) No 1924/2006. *The EFSA Journal* 2008, 825, 1-13.
- EFSA (European Food Safety Authority), 2008b. Scientific Opinion of the Panel on Dietetic Products Nutrition and Allergies on a request from Unilever PLC/NV on Plant Sterols and lower/reduced blood cholesterol, reduced the risk of (coronary) heart disease pursuant to Article 14 of Regulation (EC) No 1924/2006. *The EFSA Journal* 2008, 781, 1-12.
- EFSA (European Food Safety Authority), 2009a. Scientific Opinion of the Panel on Dietetic Products Nutrition and Allergies on a request from Danone France related to the scientific substantiation of a health claim on phytosterols and lowering/reducing blood cholesterol and reduced risk of (coronary) heart disease pursuant to Article 14 of Regulation (EC) No 1924/2006. *The EFSA Journal* 2009, 1177, 1-12.
- EFSA (European Food Safety Authority), 2009b. Scientific Opinion of the Panel on Dietetic Products Nutrition and Allergies on a request from the European Commission and a similar request from France in relation to the authorisation procedure for health claims on plant sterols/stanols and lowering/reducing blood LDL-cholesterol pursuant to Article 14 of Regulation (EC) No 1924/2006. *The EFSA Journal*, 2009, 1175, 1-9.
- McPherson TB, Ostlund RE, Goldberg AC, Bateman JH, Schimmoeller L and Spilburg CA, 2005. Phytostanol tablets reduce human LDL-cholesterol. *Journal of Pharmacy and Pharmacology*, 57, 889-896.
- Maki KC, Lawless AL, Reeves MS, Dicklin MR, Jenks BH, Shneyvas E and Brooks JR, 2012. Lipid-altering effects of a dietary supplement tablet containing free plant sterols and stanols in men and women with primary hypercholesterolaemia: a randomized, placebo-controlled crossover trial. *International Journal of Food Sciences and Nutrition*, 63, 476-482.

ABBREVIATIONS

ANCOVA	Analysis of covariance
CHD	Coronary heart disease
LDL-c	Low density lipoprotein-cholesterol
HDL-c	High density lipoprotein-cholesterol
ITT	Intention to treat
PP	Per protocol